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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,667	04/05/2005	Vasulinga Ravikumar	ISIS-5582	4970

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,667	RAVIKUMAR ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *19 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 25, 2008 has been entered.

Election/Restrictions

Claims 19 and 21-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 18, 2006.

Claim Rejections - 35 USC § 102

The claim amendments submitted 2/25/08 are sufficient to overcome the 102 rejection over Uhlmann et al.

New Claim Rejections - 35 USC § 102

Claims 1, 11, 13, 16, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rybakov et al. (Bioorganicheskaya Khimiya 1985, vol. 11, pages 1688-1689). This reference is in the Russian language; at the time this action is mailed a translation is not available; this rejection is based on the information found in the CAPLUS database record for this reference (enclosed). The translation will be mailed under separate cover.

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide and comprising a hydroxyl or protected hydroxyl at the 3' terminus. Claims 11 and 13 state that R_1, R_2 and R_3 are each H. Claim 16 defines heterocyclic base moieties that may exist within the oligomeric compound. Claim 17 states the length of the central portion of the oligonucleotide is between 8 and 30. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Rybakov et al. disclose oligonucleotides having 5' thionucleotides and comprising a 5' phosphate and 3' hydroxyl, one of which is shown in the database record. These oligonucleotides are comprised of the heterocyclic bases in claim 16. One of the oligonucleotides is 10 bases in length, meeting the limitation of claim 17. The oligonucleotides are deoxynucleotides, corresponding to the embodiments where R_1, R_2 and R_3 are each H. This oligonucleotide was subjected to a chemical degradation

procedure, which involves formation of a composition of the oligonucleotide with a pharmaceutically acceptable carrier.

Thus, Rybakov et al. disclose all limitations of and anticipate claims 1, 11, 13, 16, 17 and 20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 11-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann (US 6,033,909, of record) in view of Kostenko et al. (Nucleic Acids Research 2001), Hamma et al. (Biochemistry 1999) and Sproat et al. (Nucleic Acids Research 1987).

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide and comprising a hydroxyl or protected hydroxyl at the 3' terminus. Claim 4 recites that one position of the modified phosphate is methylated. Claim 11 states that R_1, R_2 and R_3 are each H, while in claim 12 they are each OH. Claim 13 states at least one of R_1, R_2 or R_3 may be an optionally protected substituent group, while claim 14 requires at least one optionally protected substituent group.

Claim 15 states that each X_2 is S. Claim 16 defines heterocyclic base moieties that may exist within the oligomeric compound. Claims 17 and 18 state the length of the central portion of the oligonucleotide is between 8 and 30 or 15 and 25. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Uhlmann et al. teach oligonucleotides having formula 1 (see column 3). In this formula, the internucleotide linkages can be mono- or diphosphorothioate. The V at the 5' position of the ribose can be S and the terminal R^1 can be a phosphate group, which is the equivalent of the phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide of claim 1. The Z position of the terminal phosphate groups can be C_1-C_{18} alkyl, meeting the limitation of claim 4. In the oligonucleotides disclosed by Uhlmann et al., R^2 can be hydrogen, hydroxyl or other substituents, meeting the limitations of claims 11-14. Position B is disclosed as being a conventional nucleotide base, meeting the limitations of claim 16. The oligonucleotides of Uhlmann et al. are 2-101 nucleotides in length, meeting the limitations of claims 17 and 18 and are disclosed in claim 9 as compositions with pharmaceutically acceptable carrier or diluent, meeting the limitations of claim 20. Uhlmann et al. do not teach oligonucleotides having a hydroxyl or protected hydroxyl at the 3' terminus.

Kostenko et al. teach 5'-bis-pyrenylated oligonucleotides produced by conjugating pyrene to a 5' phosphorylated oligonucleotide for the purpose of producing a fluorescent probe that can quantitatively detect hybridization.

Hamma et al. teach that producing an oligonucleotide having a 5' phosphate allows a convenient "affinity handle" for purification by strong anion exchange HPLC. In view of these teachings, one of ordinary skill in the art would recognize that predictable synthesis of oligonucleotides having a 5' phosphate is routine and this technique is used for a variety of different reasons.

Sproat et al. teach the synthesis of 5'-mercapto-2', 5'-dideoxyribonucleoside phosphoramidites that can be used to produce oligonucleotides wherein the 5' oxygen is replaced with sulfur. Because these modified nucleotides are in a form suitable for automated nucleic acid synthesis, these monomers can be substituted at any position within an oligonucleotide, including the 5' terminus. Use of these monomers in a standard synthesis protocol produces oligonucleotides having 3' hydroxyls.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce oligonucleotides comprising 5' mercapto nucleotides and a 5' phosphate as taught by Uhlmann et al. and to make such an oligonucleotide comprising a 3' hydroxyl. Based on the teaching of Sproat et al. of 5' mercapto nucleoside phosphoramidites suitable for incorporation at any point in a synthetic oligonucleotide, one of ordinary skill in the art would recognize the use of this particular monomer to be a matter of simple substitution of known equivalents that would predictably provide 5' mercapto oligonucleotides. Based on the teachings of Kostenko et al. and Hamma et al. one of ordinary skill in the art recognizes that synthesis of 5' phosphate oligonucleotides is routine in the art, therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide and a 5' phosphate is a

matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art.

Thus, the invention of claims 1, 4, 11-18 and 20 would have been obvious, as a whole, at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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